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## Adenosine A<sub>2</sub>A antagonists: neuroprotection and autophagy induction by a new compound

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Adenosine receptors A<sub>2</sub>A are a class of purinergic receptors largely expressed in dopamine (DA)-rich areas of the central nervous system. In particular, they are abundant within basal ganglia, where they modulate the activity of various neurotransmitters, including DA. Despite the lack of knowledge on their fine physiological mechanisms, it is worth to mention that A<sub>2</sub>A antagonists prevent neuronal death and dyskinesia in Parkinsonism.

A new compound, ATBI-10, binds with high selectivity to A<sub>2</sub>A receptors with antagonist activity. In the present study, by profiting of such an highly selective compound we investigated: (i) whether such a novel compound protects DA-containing neurons against the parkinsonian neurotoxin 1-methyl-4-phenylpyridinium and the dyskintogenic compound methamphetamine. (ii) The cellular mechanisms which are involved in these phenomena as a consequence of A<sub>2</sub>A receptor modulation. We carried out an *in vitro* study using two models of DA neurons PC12 and SH-SY5Y. We found that ATBI-10 at doses of 16 and 32 nM protects against DA neurotoxicity in all models, being mostly effective against MA toxicity (complete prevention). In light of the key role of autophagy in modulating the survival of DA neurons we investigated the association between A<sub>2</sub>A receptors and the autophagic pathway. We found that antagonism at A<sub>2</sub>A receptors produces an increased autophagy (increased LC3-II levels). This effect appears to be shared by all A<sub>2</sub>A antagonists.

Our data indicate that A<sub>2</sub>A antagonists are neuroprotective against a variety of insults to DA neurons and such an effect appears to be mediated by the enhancement of autophagy. We are now evaluating *in vitro* and *in vivo* whether endogenous adenosine might produce neurodegeneration by activating A<sub>2</sub>A receptors. These results indicate novel therapeutic effects of A<sub>2</sub>A antagonists and provide evidence on their mechanism of action.